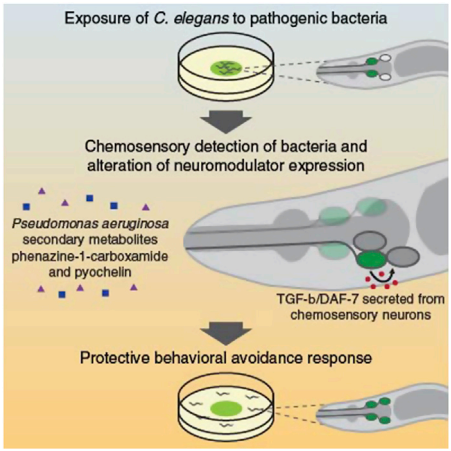
In This Issue

Cell



Psychoactive Bacteria

PAGE 267

Discriminating between pathogenic and beneficial microbes is essential for host immunity and homeostasis. Meisel et al. identify a chemosensory and neuroendocrine circuit that is activated by metabolites produced by pathogenic bacteria that directly induces avoidance behavior and promotes survival in the roundworm *C. elegans*.

Strangers in a Strange Gut

PAGE 253

To explore community dynamics within gut microbiota, Seedorf et al. colonized germ-free mice with microbiota from diverse environmental and animal habitats. Cohousing groups of mice harboring these different alien microbiota, a native mouse microbiota, and germ-free animals revealed unanticipated patterns of ecological succession, providing ways to characterize opportunists.

Shuttling Excitation

PAGE 281

In neurons, electrical activity at the membrane ultimately results in changes to nuclear gene transcription. Ma et al. discover how signals are conveyed across the cytoplasm by showing that γCaMKII transports Ca2+/CaM from cell surface to nucleus—a key step in excitation-transcription coupling. The γ shuttle is loaded at surface hotspots where CaV1 channel openings drive high-affinity Ca2+/CaM binding and nuclear translocation. Upon arrival in the nucleus, Ca2+/CaM activates a nuclear CaMK cascade that phosphorylates CREB and sparks expression of c-fos and other genes.

Love? Oxytocin, Actually

PAGE 295

Oxytocin modulates social behaviors, including interactions between genders. Nakajima et al. report the identification of a population of interneurons in the prefrontal cortex which respond to oxytocin and regulate the female social interest in male mice during estrus. Interactions with female mice or male mice during diestrus are not modulated by this system, supporting a gender-, cell-type-, and context-dependent role for oxytocin in the prefrontal cortex.

Lipid Balm for Metabolic Disease

PAGE 318

Yore et al. identify a new class of endogenous lipids that promote glucose tolerance and anti-inflammatory pathways. A subfamily of these lipids are regulated by diet, correlated with insulin sensitivity in humans. When administered in mouse models, the lipids reduce insulin resistance, suggesting new approaches for targeting metabolic disease and inflammation.

Self-Tolerance Gets Lck-y

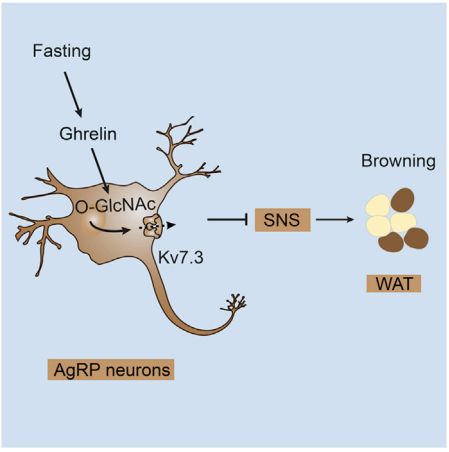
PAGE 333

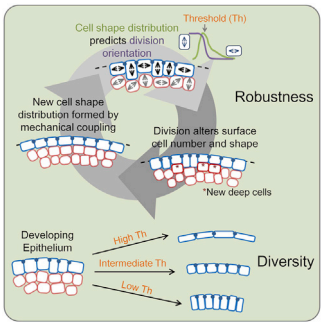
Thymocytes recognizing self-antigens with high affinity need to be eliminated from the pool of developing T cells in order to avoid autoimmunity. Stepanek et al. now find that immature T cells measure affinity for antigen through a coreceptor scanning mechanism. The T cell antigen receptor scans CD4 or CD8 coreceptor molecules until it finds one that is coupled to the Lck kinase. This is the first and rate-limiting step that eventually leads to negative selection of T cells and promotion of self-tolerance.

Brain to Brown

PAGE 306

Ruan et al. find that the enzyme O-GlcNAc transferase controls the browning of white adipose tissue by targeting a potassium channel that mediates the firing of appetite-stimulating AgRP neurons of the hypothalamus. Signals from the brain can therefore directly regulate thermogenic programs as well as whole-body energy balance and metabolic homeostasis.





Shapely Divisions

PAGE 415

Using in toto imaging, mathematical theory, and embryological perturbations, Xiong et al. investigate how epithelia with different cell shapes—squamous, cuboidal, columnar—form. They find that simple geometrical relations between tissue area, cell number, and cell volume restrict cell shapes. Shape in turn feeds back to control the number of cell divisions. This interplay ensures robust epithelial morphological development.

Replication-Triggered Proteolysis

PAGE 346

Duxin et al. develop a cell-free system to show that DNA-protein crosslinks (DPC) are repaired in a replication-dependent process. DNA replication triggers proteolysis of the DPC and replisome bypass of the remaining peptide-adduct. This DPC repair pathway does not involve the formation of double-stranded DNA breaks and thus avoids a major source of mutation and genome instability.

MegaTrans Action for Transcription

PAGE 358

Using estrogen-responsive enhancers as a model, Liu et al. find that highly active ERα-bound active enhancers recruit a large number of DNA-binding transcription factors in trans through interactions with ERα. These complexes are assembled in situ, and required for enhancer RNA transcription, recruitment of coactivators, and chromatin modifying enzymes. This model provides an explanation for the long-standing conundrum that approximately half of DNA-binding regions for transcription factors examined by the ENCODE project do not harbor cognate DNA motifs.

Super-Enhanced Gated Communities

PAGE 374

The pluripotent state of embryonic stem cells is produced by active transcription and repression of genes that control cell identity. Dowen et al. show that both super-enhancer-driven cell identity genes and repressed lineage-specifying genes occur in insulated neighborhoods formed by the looping of two interacting CTCF sites co-occupied by cohesion. The integrity of these structural neighborhoods is important for proper expression of nearby genes.

ESCRT Service for the NPC

PAGE 388

Webster et al. discover a quality control role for the endosomal sorting required for transport (ESCRT) machinery in surveillance of nuclear pore complex assembly (NPC) as well as proper compartmentalization of the nucleus. Defective or improperly assembled NPCs are sequestered away in a specialized compartment of yeast mother cells, thereby supporting daughter cell viability.

Can You DIGGIT?

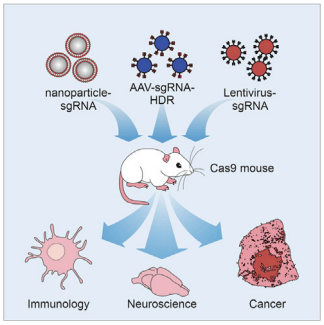
PAGE 402

In complex genetic disease, identifying a mutation's downstream molecular effects represents a critical, but daunting task. Chen et al. introduce a new integrative, network-based algorithm (DIGGIT) and demonstrate its application to unbiased discovery of genetic alterations driving mesenchymal differentiation in glioblastoma. They identified two new loci missed by statistical analyses: KLHL9 and CEBPD. Analysis of breast cancer and Alzheimer's disease networks further demonstrated that DIGGIT is a generalizable pipeline for both germline and somatic variants.

How to Make a β Cell

PAGE 428

The treatment of diabetes has been hampered by the lack of a renewable source of functional human pancreatic β cells. Pagliuca et al. establish a scalable, in vitro differentiation protocol for generating functional β cells from human pluripotent stem cells. These β cells respond to multiple glucose challenges in vitro and reverse hyperglycemia in mice after transplantation. This advance presents an important opportunity for therapeutic development and disease modeling in diabetes.



Mouse Engineering Made CRISPR

PAGE 440

Platt et al. generate two strains of CRISPR-Cas9 knockin mice and demonstrate gene editing in the brain, immune cells, vasculature, and the lung using viral and nonviral delivery of sgRNAs. A single AAV vector containing sgRNAs and a donor template induce p53 and Lkb1 double knockout, as well as oncogenic Kras, leading to lung adenocarcinoma formation. The Cas9 mice enable diverse genome engineering applications in biology and disease modeling.